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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/452,843	05/30/1995	ALESANDRO SETTE	014137-00802	5698
26111	7590	02/25/2004	EXAMINER	
STERNE, KESSLER, GOLDSTEIN & FOX PLLC 1100 NEW YORK AVENUE, N.W. WASHINGTON, DC 20005			DIBRINO, MARIANNE NMN	
			ART UNIT	PAPER NUMBER

1644

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/452,843	SETTE ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 2/13/02, 7/1/02, 3/12/02, 2/27/03 & 11/18/02.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 176-233 is/are pending in the application.
- 4a) Of the above claim(s) 178, 179, 182-190, 193, 196, 197, 202 and 204-233 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 176, 177, 180, 181, 191, 192, 194, 195, 198-201 and 203 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>10/2/02 & 3/19/03</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The request filed on 2/13/02 (Paper No. 37) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/452,843 is acceptable and a CPA has been established. An action on the CPA follows.
2. Applicant's amendments filed 7/01/02 and 3/12/02 (Papers No. 43 and 38, respectively) and Applicant's responses filed 2/27/03 and 11/18/02 (Papers No. 51 and 47, respectively) are acknowledged and have been entered.
3. (a). Applicant is reminded that since Applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for the prosecution on the merits. Accordingly, claims 178, 179, 187-190, 202 and 204-223 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP 821.03. Newly submitted claims 178, 179, 187-190, 202 and 204-233 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 179, 187-190, 210-221 are methods comprising using a nucleic acid, belonging to non-elected Group II, classified in Class 435, subclass 69.1. Applicant is reminded that the elected invention being examined is classified in Class 514, subclasses 15 and 16. Claims 178, 202, 204-209 and 222-233 are drawn to non-elected peptide species of elected Group I.

(b). Applicant's election in Applicant's response filed 7/2/03 of species of an oligopeptide less than 15 amino acid residues in length comprising the elected peptide APAPAPSWPL (SEQ ID NO: 14), wherein the evaluating step is for the ability to induce an HLA-B7 restricted CTL response in vitro, and method comprising administering a vaccine is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Accordingly, claims 182-186, 193, 196 and 197 are withdrawn from consideration as being directed to a non-elected invention (non-elected species of elected Group I). See 37 CFR 1.142(b) and MPEP 821.03.

Claims 176, 177, 180, 181, 191, 192, 194, 195, 198-201 and 203 read upon the elected species and are currently being examined.
4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant is required to provide SEQ ID NO. for the sequences listed in the Figures.

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Applicant's comments on page 5 of Applicant's amendment filed 7/01/02 has been noted by the Examiner, but is not persuasive. The sequences in Figures 1 and 2 contain 4 or more defined amino acid residues.

5. Applicants are required to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, in the Brief Description of the Drawings for Figures 1 and 2).

6. The oath or declaration is defective.

A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: a post office address was not provided for the second inventor.

7. The amendment filed 3/12/02 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: SEQ ID NO: 31 and 34, in the CRF which are 8-mer and 11-mer peptides with a P2 Pro and a carboxy-terminal Ile/Leu.

Applicant is required to cancel the new matter in the reply to this Office Action.

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 176, 177, 180, 181, 191, 192, 194, 195 and 198-200 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

This rejection is a new matter rejection.

The added material which is not supported by the original disclosure is as follows:

(1) A method comprising binding an HLA-B7 molecule with a peptide comprising an epitope of p53 comprising contacting the said HLA-B7 molecule with a peptide 8-11 amino acid residues in length having a Pro at position 2 and a Leu or an Ile at the carboxy terminus of the said peptide, including SEQ ID NO: 31 and 34, i.e., 8 and 11-mer peptides.

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Applicant points to support for the position 2 and carboxy-terminal hydrophobic amino acid residue motif on page 2 at lines 19-23 and page 3 at lines 2-7 and 13-15 and on page 4 at lines 21-23 and for support for 8-11 amino acids on page 3 at lines 5-7 and 19-20 of the instant specification. However, the specification on page 2 of the said location discloses that immunogenic peptides are about 9 to 10 residues in length and comprise conserved residues at certain positions such as proline at position 2 and an aromatic residue (e.g., Y, W, F) or hydrophobic residue (e.g., L, I, V, M, or A) at the carboxy terminus. The disclosure on page 3 at the specified locations is that the oligopeptides of the invention are less than about 15 residues in length and usually consist of between about 8 and about 11 residues, preferably 9 or 10 residues, that two or three amino acid residues at particular positions in the peptide provide contact with HLA molecules and define a motif, that "motif" refers to the pattern of residues in a peptide of defined length, usually about 8 to about 11 amino acids, which is recognized by a particular MHC allele. There is no disclosure of a peptide of about 8-11 amino acid residues which has the specified motif, and there is no disclosure as to whether the motif of position two is at position two of an 8-mer peptide and the carboxy-terminus of an 8-mer peptide or at position 2 of an 11-mer peptide and the carboxy-terminus of an 11-mer peptide.

10. Claims 176, 177, 180, 181, 191, 192, 194, 195, 198-201 and 203 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the . . . claimed subject matter", *Vas-Cath, Inc. V. Mahurkar*, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed invention.

The instant claims encompass a method for binding to HLA-B7 molecules peptides of between 8 and 11 amino acid residues in length, or wherein the said peptide is endogenously processed from a peptide less than 15 amino acid residues in length, derived from p53 tumor antigen wherein amino acid residues at anchor positions are specified as P2 Pro and carboxy-terminal Leu or Ile. The instant claims further encompass the said method wherein the peptide may be evaluated in vitro or not for the ability to serve as a target for HLA-B7 restricted CTL, or wherein further method steps comprising in vitro or in vivo elicitation of CTL and the administration of a vaccine composition comprising the said peptide, including the peptides recited in instant claim 201 and the elected species APAPAPSWPL from p53 tumor antigen. The specification discloses that two amino acids recited in the claim are pertinent to HLA binding of said peptides for 9 and 10-mer peptides. However, the art recognizes that in order to be used for generating an immunogenic response that said peptide must bind MHC and also

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present an epitope recognized by T cells. The art recognizes that the T cell epitope differs from the amino acids pertinent to MHC binding. There is no written description in the specification of the amino acids that constitute the T cell epitope in the peptide recited in the claim. Therefore, the skilled artisan cannot envision the detailed structure of the encompassed peptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. In the instant application, the amino acid itself or isolated peptide is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein. See *The Regents of the University of California v. Eli Lilly and Company*, 43 USPQ2d 1398, 1404-7 (Fed. Cir. 1997). In *University of California v. Eli Lilly and Co.*, 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995) the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, *id.* at 1240. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials. . .conception has not been achieved until reduction to practice has occurred", *Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd.*, 18 U.S.P.Q.2d 016 (Fed. Cir. 1991). Attention is also directed to the decision of *The Regents of the University of California v. Eli Lilly and Company* (CAFC, July 1997) wherein is stated: "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA." See *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606.

10. Claims 176, 177, 180, 181, 191, 192, 194, 195, 198-201 and 203 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of binding an HLA-B7 molecule with a peptide comprising an epitope of p53 comprising contacting said HLA-B7 molecule with a peptide of 9-11 amino acid residues in length that has a Pro at position 2 of the said peptide and a Leu or Ile at the carboxy terminus of the said peptide and further comprising evaluating the said peptide in vitro for the ability of the said

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peptide to serve as a CTL target in vitro, does not reasonably provide enablement for the said method further comprising testing in vivo or eliciting an immune response in vivo, including a step of administering a vaccine composition comprising the said peptide, and including wherein the peptide is 8 amino acid residues in length, and including wherein the epitope is fully defined, but the peptide is not. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification does not disclose how to practice the method of inducing an immune response, including as a vaccine composition for treatment or for prophylaxis, with a peptide comprising an epitope consisting of 8-11 amino acid residues that will bind to an HLA-B7 molecule and induce an HLA-B7-restricted immune response. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass methods of inducing an immune response where no immune response will occur.

For purposes of examination, the instant claims are given their broadest reasonable interpretation.

The process steps of the instant claims provide a peptide that comprises an epitope that comprises a motif and a step of inducing an immune response in vitro or in vivo, and in addition, of endogenously processing the peptide from an oligopeptide less than 15 amino acid residues in length prior to binding recited in claim 180. The instant claims encompass the said method wherein the peptide may be evaluated in vitro or in vivo for the ability to serve as a target for HLA-B7 restricted CTL, or wherein further method steps comprising in vitro or in vivo elicitation of CTL and the administration of a vaccine composition comprising the said peptide, including the peptides recited in instant claim 201 and the elected species APAPPSWPL from p53 tumor antigen. The specification discloses that two amino acids recited in the claim are pertinent to HLA binding of said peptides for 9 and 10-mer peptides. However, it is unpredictable whether said peptide would bind to HLA and induce a CTL response, i.e., it is unpredictable that said peptide that binds to HLA would be immunogenic. The specification is not enabling for the claimed method whereby an immune response is generated, including administering the peptide as a vaccine composition for prophylaxis or treatment.

The specification provides no evidence that the motif-bearing peptides of the claimed method are immunogenic. Celis et al (Molecular Immunol. 3: 1423-1430, 1994, IDS reference) teach that in order to establish whether a peptide is immunogenic said peptide needs to be tested in assays that actually establish that a peptide is immunogenic. Further, although *experimental* ranking schemes are available for predicting relative binding strengths of some HLA binding nonapeptides, and assays are available to test the binding of peptides to HLA, an undue amount of experimentation would be involved in determining peptides from the many possibilities that would be capable of binding to HLA and inducing a CTL response. Celis et al teach that "In

addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether any of these peptides can function as effective CTL antigens." Ochoa-Garay et al (Molecular Immunol. 34: 273-281 1997, IDS reference) teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs. In addition, our data show that variables such as CTL precursor frequency, peptide hydrophobicity and stability can influence the in vitro induction of CTL responses (especially page 279, last sentence and continuing onto page 280). Karin et al (J. Exp. Med. 180: 2227-2237, 1994, IDS reference) teach that amino acids in an MHC binding peptide that are not the amino acids which participate in MHC binding can have a profound effect on whether or not a peptide is immunogenic. The claimed invention recites a motif wherein residues not involved in MHC binding are not specified except in claims 110-113 wherein amino acid residues not permitted at one non-MHC binding position in the peptide are specified. Karin et al teach that a single substitution in an amino acid, wherein said amino acid plays no role in MHC binding can completely abrogate the immunogenicity of an otherwise immunogenic peptide (especially Summary and Table 1). Thus Karin et al establish that amino acid residues not recited in the claimed peptide (i.e., amino acid residues not involved in MHC binding of a peptide) will play a pivotal role in determining whether the peptides recited in the claims are immunogenic.

Kast et al (Eur. J. Immunology 1993 23: 1189-1192) teach that the amino acid residues can exert important effects upon the binding capacity of a peptide, and hence by extension, to potential immunogenicity. DiBrino et al (J. Immunology 151(11) 5390-5935, 1993) teach that the presence of anchor residues is not sufficient for binding to HLA because peptides with optimal amino acid residues at anchor positions failed to bind. Van der Most et al (J. Immunol. 1996, 157: 5543-5554 and Virology 1998, 240: 158-167) teach that although an antigenic protein may contain multiple motif-fitting peptides, CTL responses are usually directed against a very limited number of immunodominant epitopes and that immunodominance appears to be determined by a variety of factors including binding affinity to HLA (and motif binding peptides bind with a wide range of affinities due to secondary anchor residues and secondary effects), intracellular processing of peptides determines whether at which level a particular peptide will be presented at the cell surface, and holes in the T cell repertoire restrict CTL responses. Van der Most et al also teach that a peptide from NP with the second highest binding affinity ($IC_{50} = 4.8nM$) after the immunodominant peptide for L^d , is not recognized by LCMV-restricted CTLs. Chang et al (J. Immunol. 1999, 162: 1156-1164) teach a peptide that was immunogenic in only a single patient despite similar HLA-binding affinity. Vitiello et al (J. Immunol. 1996, 157: 5555-5562) teach the importance of not only binding affinity, but also of availability of specific TCRs and antigen processing in the shaping of the final repertoire of CTL specificities. Bergman et al (J Virol. 1994, 68(8): 5306-5310) teach a discrepancy between antigenicity and immunogenicity, i.e., failure to induce CTL despite highly efficient recognition in vitro.

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In addition, Chaux et al (Int. J. Cancer 77 538-542, 1998) teach that it is unclear if peptides from tumor specific proteins possessing anchor residues for binding to class I MHC produce CTL responses in patients vaccinated with the said peptides. Chaux et al further teach that detection of such CTL may require very sensitive detection assays, rather than the conventional assays disclosed in the instant specification. In addition, Chaux et al teach that it is unclear whether the results seen in vitro are predictive of what occurs in vivo in humans.

Anderton (Immunology 2001 104 367-376) teaches that in vivo use of altered peptide ligands is unpredictable and dangerous in outbred human populations (especially paragraph spanning columns 1 and 2 on page 370).

Further, claim 180 recites the limitation of wherein prior to the contacting step, the peptide is endogenously processed from an oligopeptide less than 15 amino acid residues in length. The length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A", "F") located at opposite ends of the binding groove of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27.) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo, et al at page 366, column 1 lines 1-10, of record) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends." (Engelhard at page 14, column 1, lines 23-27, of record). The minimum amount of peptide required to span the binding groove and make favorable contacts with their N-and C-termini may be dependent upon the sequence of the peptide itself since different amino acid residues have different physicochemical properties, and may be dependent upon the identity of the additional amino acids, since these residues may make a negative contribution to binding. Accordingly, there is a high level of unpredictability in designing/selecting longer sequences that would still maintain binding function, and applicant does not provide direction or guidance to do so. Shastri et al (J. Immunology 1995, 155: 4339-4346) teach that presentation of endogenous peptide/MHC class I complexes is profoundly influenced by specific C-terminal flanking residues. Maier et al (Immunogenetics 40: 306-308, 1994) teach that peptides that bind to HLA-B7 molecules are 9-11 amino acid residues in length, i.e., at least 9 amino acid residues in length.

It would require undue experimentation to determine which of the trillions of peptides encompassed by the claimed invention are immunogenic and which are not. Further, synthetic peptides that are chosen on the basis of scanning the protein of interest for potential peptide sequences that have a supermotif for binding to an HLA molecule or molecules may not induce a CTL response due to lack of Th support for CTLp to CTL.

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There is insufficient guidance in the specification as to how to practice the method of the instant invention. There is no disclosure in the specification as to making and/or using a peptide comprising an epitope with the motif recited in the instant claims and capable of binding to HLA-B7 and inducing an immune response, which amino acid residues at non-anchor positions are permissive for binding of the peptide to HLA molecules and which binding peptides would contain a T cell epitope and be immunogenic. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 176, 177, 180, 181, 191, 192, 194, 195, 198-201 and 203 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 176 is indefinite in the recitation of “and comprises an epitope of p53 (SEQ ID NOS: 31-34)” because it is not clear what is meant. SEQ ID NO: 31-34 are motif peptides which are not necessarily from p53.

13. With regard to application of prior art, the filing date of the instant claims is that of the instant application, i.e., 5/30/95, because the scope of the claimed invention is not disclosed in parent application 08/344,824, nor in parent application 08/278,634. The parent application does not support the claimed method; in minimis, the parent application does not provide support for a method comprising binding an HLA-B7 molecule with a peptide comprising an epitope of p53 comprising contacting the said HLA-B7 molecule with a peptide 8-11 amino acid residues in length having a Pro at position 2 and a Leu or an Ile at the carboxy terminus of the said peptide, including SEQ ID NO: 31 and 34, i.e., 8 and 11-mer peptides, said parent applications do not disclose the elected species APAPAPSWPL recited in instant claim 201.

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a

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later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103[®] and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 176, 177, 180, 181, 191, 192, 195, 201 and 203 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zakut-Houri et al (EMBO J. 4(5), 1985, pages 1251-1255, of record), Harlow et al (Molec. Cell. Biol., 5(7), 1985, pages 1601-1610, of record) Harris et al (Mol Cell Biol., 6(12), 1986, pages 4650-4656, of record) or Lamb et al (Molec. Cell. Biol., 6(5), 1986, pages 1379-1385, of record) each in view of Hill et al (Nature 360(3), 1992, pages 434-439, of record), Huczko et al (J. Immunol., 151(5), 1993, pages 2572-2587, of record).

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al teach the amino acid sequence of the human tumor antigen p53.

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al do not teach a method for making an immunogenic peptide comprising APAPAPSWPL.

Hill et al teach that peptides that are T cell epitopes for HLA-B35 have a position 2 Pro and a Leu at the carboxy terminus. Hill et al teach searching sequences of known antigens for potential epitopes based upon motif amino acids and synthesis of said potential epitopes, e.g., peptides of 8-10 amino acid residues in length (especially column 2 on page 434, last paragraph and Table 2, tr15 and tr20).

Huczko et al teach that peptides that bind to HLA-B7 have Pro at position 2 and L at the carboxy terminus and are 9-11 amino acid residues in length.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have scanned the p53 tumor antigen amino acid sequence of Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al for subsequences such as APAPAPSWPL that possess a motif as taught by Hill et al, such as the motif taught by Huczko et al, for binding to a HLA class I allele expressed in populations of humans, including HLA-B7, to have made the said subsequences in a length compatible with binding to HLA class I molecules as taught by Hill et al and Huczko et al (i.e., 9-11 amino acid residues in length) and to have tested complexes of the peptide/HLA molecules for their ability to be bound by HLA-B7 in vitro recognized by CTL restricted by said HLA molecules in vitro.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to narrow the number of peptides from the p53 sequence taught by Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al that need to be synthesized by using the motifs as taught by Hill et al such as for the HLA-B7 binding peptide motif taught by Huczko et al and to provide potential CTL epitopes as taught by Hill et al.

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16. Claims 176, 177, 180, 181, 191, 192, 195, 201 and 203 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zakut-Houri et al (EMBO J. 4(5), 1985, pages 1251-1255), Harlow et al (Molec. Cell. Biol., 5(7), 1985, pages 1601-1610) Harris et al (Mol Cell Biol., 6(12), 1986, pages 4650-4656) or Lamb et al (Molec. Cell. Biol., 6(5), 1986, pages 1379-1385) each in view of Sidney et al (J. Immunol. 154, January 1, 1995, pages 247-259), all of record.

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al teach the amino acid sequence of the human tumor antigen p53.

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al do not teach a method for making an immunogenic peptide comprising APAPAPSWPL.

Sidney et al teach peptides with HLA-B7-like supermotif, i.e., Pro at position 2 and hydrophobic/aromatic amino acid residues at the C terminus (especially abstract). Sidney et al teach that the said peptides bind to multiple class I HLA alleles such as HLA-B701, HLA-B5101, HLA-B5301 and HLA-B3501 (especially Table III). Sidney et al teach peptide-based immunizations for the treatment of viral or parasitic infections and cancers and that elicitation of specific class I restricted CTL responses may be crucial in controlling tumor growth and/or prevention of metastasis (especially paragraph spanning pages 247 and 248). Sidney et al further teach that discovery of peptide epitopes capable of broad cross-reactivity among most or all members of the B7-like supertype family of alleles could be of significant practical importance in the development of peptide-based vaccination strategies (especially last paragraph on page 248 before Materials and Methods section). Sidney et al also teach production of synthetic peptides. Sidney et al teach that good binding is equivalent to an IC50 of less than 500 nM (especially line 8 of column 1 on page 252).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have scanned the tumor antigen p53 amino acid sequence of Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al for subsequences, including APAPAPSWPL, which comprise a binding motif for any of the HLA alleles, including HLA-B701, HLA-B5101, HLA-B5301 and HLA-B3501, which have the B7-like supermotif of Sidney et al, including Pro at position 2 and Leu at the carboxy terminus, to make the said subsequences in a length compatible with binding to HLA class I molecules (i.e., 9, 10 or 11 amino acid residues in length), to complex said subsequences with the class I HLA molecules in vitro and to test in vitro for CTL responses to said peptides when in complex with HLA class I molecules.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to narrow the number of peptides from the p53 sequence taught by Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al that need to be synthesized by using the motifs as taught by Hill et al for HLA-B7 binding peptides taught by Huczko et al and to provide potential immunogenic peptides for vaccines as taught by Sidney et al.

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17. Claims 176, 177, 180, 181, 191, 192, 195, 201 and 203 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zakut-Houri et al (EMBO J. 4(5), 1985, pages 1251-1255), Harlow et al (Molec. Cell. Biol., 5(7), 1985, pages 1601-1610) Harris et al (Mol Cell Biol., 6(12), 1986, pages 4650-4656) or Lamb et al (Molec. Cell. Biol., 6(5), 1986, pages 1379-1385) each in view of Hill et al (Nature 360(3), 1993, pages 434-439) and Maier et al (Immunogenetics 4); 306-308, 1994, of record).

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al teach the amino acid sequence of the human tumor antigen p53.

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al do not teach a method for making an immunogenic peptide comprising APAPAPSWPL.

Hill et al teach that peptides that are T cell epitopes for HLA-B35 have a position 2 Pro and a Leu at the carboxy terminus. Hill et al teach searching sequences of known antigens for potential epitopes based upon motif amino acids and synthesis of said potential epitopes, e.g., peptides of 8-10 amino acid residues in length (especially column 2 on page 434, last paragraph and Table 2, tr15 and tr20). Hill et al also teach peptides that bind to HLA-B51 have position 2 Pro and Val or Ile at the carboxy terminus (especially Figure 1a, peptides cp6, Is6 and sh1, and Table 2) and that these peptides also bind to HLA-B53.

Huczko et al teach that peptides that bind to HLA-B7 have Pro at position 2 and L at the carboxy terminus.

Maier et al teach the motif for peptide binding to HLA-B7 is Pro at position 2 and L at the carboxy terminus. Maier et al further teach that the motifs provide valuable information on potential antigenic eptiopes that might be used in subunit vaccine strategies against viral infections.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have scanned the p53 tumor antigen amino acid sequence of Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al for subsequences such as APAPAPSWPL that possess a motif as taught by Hill et al, such as the motif taught by Huczko et al and Maier et al for binding to a HLA class I allele expressed in populations of humans such as HLA-B7, to have made the said subsequences in a length compatible with binding to HLA class I molecules (i.e., generally 9, 10 or 11 amino acid residues in length) and to have tested the peptides in vitro for binding and the ability to be recognized by CTL in vitro.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to narrow the number of peptides from the p53 sequence taught by Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al that need to be synthesized by using the motifs as taught by Hill et al for HLA-B7 binding peptides taught by Huczko et al and Maier et al to provide potential immunogenic peptides for vaccines as taught by Maier et al.

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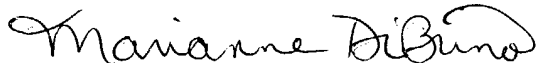
18. The references crossed out in the Form 1449 filed 10/2/02 have not been considered because they have not been provided in parent case serial no. 08/344,824. Applicant is requested to provide these references.

Applicant is advised that the date of the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday and Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chan Y Christina, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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February 20, 2004



CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Application No.: 08/452,843

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS
CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE
DISCLOSURES**

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☒ 7. Other: Applicant must provide sequence id nos for the sequences appearing in Figures 1 and 2 which contain 4 or more defined amino acid residues.

Applicant Must Provide:

- ☒ ~~An initial or~~ substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ ~~An initial or~~ substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
-
- ☒ A statement that the content of the paper and computer readable copies are the

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same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

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